Lymphoma Incidence in Italian Military Personnel Involved in Operations in Bosnia and in Kosovo

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Background

The question of whether there has been an increase in leukaemia/lymphoma or other cancers in occupants of or peacekeepers deployed in the Balkans has been a source of argument of a similar order and type as the question of increases in leukaemia/lymphoma and birth defects in Iraq. In the case of the Balkans, there is very little hard evidence (e.g. cancer registry data) which is available for independent scrutiny, and indeed some of the problems associated with the kinds of population movements that follow a major conflict would make such analyses very difficult. There has been a leak of a table of cancer incidence in Sarajevo from the cancer registry there which suggests a more than 10-fold increase in leukaemia and lymphoma (Table 1 below) even allowing for a doubling in the base population. This information was given to the Royal Society as evidence last year but was not included in their report or followed up by them.

Tumour Site	1995	1996	1997	1998	1999	2000
Mouth and Throat	1 (1.1)	-	--	2 (2.1)	4 (4.3)	4 (4.3)
Digestive	15 (16.0)	50 (53.2)	36 (38.3)	55 (58.5)	68 (72.4)	82 (87.3)
Respiratory	12 (12.8)	15 (16.0)	20 (21.3)	34 (36.2)	44 (46.8)	51 (54.30
Skin and ligaments	-	2 (2.1)	1 (1.1)	10 (10.6)	8 (8.5)	9 (9.6)
Breast	3 (3.2)	11 (11.7)	14 (15.0)	29 (30.9)	34 (36.2)	37 (39.4)
Urogenic	8 (8.5)	8 (8.5)	11 (11.7)	18 (19.2)	27 (28.7)	28 (29.6)
Eyes	3 (3.2)	-	1 (1.1)	2 (2.1)	1 (1.1)	4 (4.3)
Lymphatic and Blood	1 (1.1)	6 (6.4)	1 (1.1)	7 (7.4)	19 (20.2)	26 (27.7)
Divers	-	1 (1.1)	11 (11.7)	18 (19.2)	11 (11.7)	7 (7.4)
All above	43 (45.3)	93 (99.0)	95 (101.0)	175 (186.)	216 (230)	248 (264)

Table 1 Cancer incidence in Sarajevo 1996-2000. Cases (crude rates per 100,000). (Source: Sarajevo Tumour Registry)

In addition, there has been anecdotal evidence of increases in leukaemia/lymphoma in the Italian and Portuguese peacekeepers and these have led to misleading statements from the authorities. Recently in a letter to Caroline Lucas MEP, a UK government minister, Dr Lewis Moonie suggested that 42 leukaemia deaths per 100,000 peacekeepers was a reasonable sum and that therefore the handful of deaths observed should be seen as a normal situation. Table 2 shows the numbers of deaths from leukaemia by age in males in England and Wales in 1998 and calculates the overall rate.

Age	Observed	Male pop.	Rate per 10,000
20-24	27	1984394	0.136
25-29	24	2168819	0.110
30-34	24	1967765	0.127
35-39	41	1711844	0.239
40-44	27	1760461	0.153
45-49	49	1700017	0.288
50-54	86	1360926	0.631
55-59	106	1281777	0.827
60-64	138	1228076	1.123
65-69	217	1129274	1.921
70-74	316	919901	3.435
total	1055	17213254	Rate = 6.12e-5
			Rate = 0.612 per 10,000

Table 2 Leukemia deaths in men in England and Wales in 1998 by age group

The value, 0.612 is for all ages 20-75 combined and is not correct for soldiers who are younger. Leukaemia rates increase markedly in people above 50 as you can see from the table and this would suggest a higher expected number of deaths if this large age group were used as a basis for any comparison. It is unlikely that there would have been many soldiers older than 40. Assuming an age range of 20-40 (which is conservative) there should be 0.15 deaths per 10,000 exposed per year (i.e. the death rate in the men aged 20-40 is about 116/7832822 = 1.48 E-5 which is 0.148 per 10,000 per year. So in the year since the bombing we should expect approximately 0.15 per 10,000 or 1.5 deaths in 100,000).

In January 2001, Nippon TV were told there were 7 leukaemia deaths in Italian Kosovan peacekeepers (assume 50,000) and more recently Eddie Goncalves, a journalist in Portugal, reported 5 deaths from leukaemia in the Portuguese Kosovan peacekeepers (5 deaths in 10,000 with two in the 20-30 age group). Thus in those groups we observe 12 leukaemia deaths where 0.9 are expected, a relative risk of 13. Even if we use a two-year period since the war the Relative Risk is still 6.5 However, there has recently been an official investigation of cancer in the Italian Balkan peacekeepers and the incidence of cancer in this group has been tabled and assessed. The analysis of the findings made by the Italian epidemiologists concluded that there was no significant increase in cancer but there was a confusing reference to a 'non-significant' increase in lymphoma. I want to look more closely at these results and the analysis. But first I will briefly examine the biologically likely consequences of DU exposure and develop a prior hypothesis.

The radiological consequence of DU exposure

The dissonance between the conventional (ICRP/Royal Society) analysis of the health effects of DU exposure and those advanced by independent researchers and the new models of the European Committee on Radiation Risk (ECRR) pivots on the type of exposure involved (Busby 2000, 2001) The ICRP model assumes uniform and averaged deposition of ionisation in the whole body or organ, leading to a very low overall dose. The independent model argues that because of the micron diameter particulate nature of the DU, there will be high local and fractionated doses to cells close to the particles and no doses to the majority of cells more distant than the 30 micron range of the particles. This has two consequences. First, the cell dose is in the dose-squared region of the dose-response curve, and thus unrepairable chromosome double strand breaks are very likely. Second, the fractionation of doses in time, makes it highly probable that Second Event enhancement of mutation hazard will occur. These arguments are reviewed in Busby 2001.

It is of some interest, however, to consider which of the organs/ tissues of the body will be most likely to suffer damage from particulate DU and thus predict the cancer sites most likely to suffer increased risk. From the particle inhalation route we might expect irradiation of the lung and upper respiratory tract with possible increases in lung cancer and respiratory tract tumours and then following translocation to the lymphatics, lymphoma and to a lesser extent leukaemia. From the ingestion route, it is possible that colon cancer might result, and excretion of the Uranium through the kidneys might result in increased incidence of kidney cancer. Increases in incidence of cancer in any or all of these site would be consistent with exposure to particulate DU.

The Italian Report: *Seconda Relazione Della Commissione Institiuta Dal Ministro Della Difesa Sull' Incidenza di Neoplasie Maligne tra I Militari impiegati in Bosnia 28 Maggio 2001*

David Coggon reviewed the results of this report for the members of the UK DU Oversight board and since he has outlined the case made by the authors of the report, I give his comments below in full.

Coggon's review

I have now had a chance to look at a preliminary report of this study in English, dated 19 March 2001.

The report describes a cohort study of Italian military personnel who were followed up from the date of their first mission to Bosnia or Kosovo until 31 January 2001. Cancer incidence, ascertained from various sources including voluntary unsolicited reports, was compared with that in the male populations covered by Italian tumour registries.

With allowance for a minimum latent interval of 12 months from first deployment, there were 18 cases of cancer in the cohort as compared with 32 expected. These cases of cancer included one non-Hodgkin's lymphoma (3.3 expected), six Hodgkin's lymphoma (2.2 expected) and one acute lymphoplastic leukaemia (0.42 expected).

The study has two major but unavoidable limitations. First, cases of cancer in the cohort were ascertained from different sources than for the comparison population. This could give rise to bias in either direction.

Second, the follow-up of the cohort was extremely short. This meant that there was greater statistical uncertainty because relatively few cancers had occurred. Furthermore, if the cohort was exposed to a cancer hazard in Bosnia or Kosovo, it is possible that the effects of that exposure would not yet be manifest (because of the latent interval that often occurs between exposure to a carcinogen and the subsequent manifestation of the disease)

Overall, the findings seem unremarkable. The statistically significant deficit of deaths from cancer overall is probably in part because of a "healthy worker effect". Military personnel known to have cancer would not have been sent on missions, and would have been selectively excluded from the cohort.

I would like now to examine these results and suggest, contrary to Prof. Coggon's view, that they show a highly significant excess risk from lymphomas and that the temporal spectrum of the disease suggests that this was a result of their periods of duty in the areas where DU had been used. The statistically significant excess of lymphoma was recorded in Table 7 of the original Italian language version of the report which recorded 5 cases of non-Hodgkin lymphoma and 11 cases of Hodgkin's lymphoma, contrary to Prof. Coggon's assertion above.

The results given in the Italian version of this report are given below in Table 3.

Table 3 *Seconda Relazione Della Commissione Institiuta Dal Ministro Della Difesa Sull'*

Incidenza di Neoplasie Maligne tra I Militari impiegati in Bosnia 28 Maggio 2001: Table 5
Descrizione dei case accertati al 30/04/2001

No	Arma	Age Diag	Diagnosis	diag-date	mission	lag	location	days there
31721	E	22	Nhl	2/24/00	5/13/99	9	Sarajevo	109
1175	E	25	Nhl	7/22/99	8/31/98	11	Sarajevo	183
24744	E	25	Nhl	11/5/99	10/12/96	31	Sarajevo&Drakova	277
2763	E	30	Nhl	11/27/96	7/3/96	4	Sarajevo	125
39280	E	31	Nhl	12/16/96	12/4/95	12	Sarajevo	101
23732	E	22	Hl	11/30/99	4/1/99	7	Pec	64
19481	E	22	Hl	10/20/00	5/22/99	17	Pec	137
12425	E	23	Hl	3/2/99	1/27/97	26	Sarajevo	388
25808	E	23	Hl	11/27/00	6/7/99	17	Sarajevo	80
34327	E	24	Hl	5/9/00	10/21/99	7	Pec	90
29920	E	26	Hl	12/18/00	9/23/96	51	Sarajevo&Drakova	358
24859	E	28	Hl	9/16/98	5/9/96	28	Sarajevo	147
24562	E	32	Hl	4/7/00	1/13/98	27	Sarajevo	197
38311	E	36	Hl	3/1/98	4/28/97	11	Sarajevo	98
17563	E	39	Hl	7/24/00	2/23/98	29	Sarajevo	157
22191	Cc	42	Hl	1/30/01	10/5/99	15	Sarajevo	177
5649	E	22	All	5/27/99	10/14/97	19	Sarajevo	223
37516	E	23	All	4/27/99	11/18/98	5	Sarajevo	102
13297	E	21	Thyroid	10/6/98	11/27/97	11	Sarajevo	161
18931	E	26	Thyroid	3/22/00	3/3/99	12	Sarajevo	162
4584	Am	33	Thyroid	7/13/00	8/5/99	11	Dakovika	60
31984	E	29	Intestino	4/17/00	6/8/96	46	Sarajevo	161
7788	Cc	41	Intestino	10/9/00	12/30/96	46	Sarajevo&Mostar	419
37392	Cc	47	Intestino	8/15/99	10/22/97	22	Sarajevo	201
11745	E	56	Intestino	3/20/00	10/21/96	41	Sarajevo	113
33360	E	26	Brain	21/09/00	26/06/97	39	Banja-Sarajevo	109
36398	E	43	Brain	04/09/99	05/01/96	44	Sarajevo	107
3318	E	23	Melanoma	05/04/00	27/11/97	28	Sarajevo	118
8387	CC	29	Melanoma	18/05/98	09/12/96	17	Sarajevo	108
4046	E	38	Melanoma	06/05/00	12/03/97	38	Sarajevo	68
13357	E	23	Lung	29/06/00	02/10/98	21	Sarajevo	180
31058	E	26	Testicle	13/10/99	26/08/97	26	Sarajevo	167
36501	E	39	Pharynx	14/04/00	09/01/96	51	Sarajevo-Pec	240
10167	E	36	Larynx	12/01/00	19/09/96	40	Sarajevo-Klina	313
16436	AM	47	Pulmon.	28/04/00	10/02/00	2.5	Sarajevo	

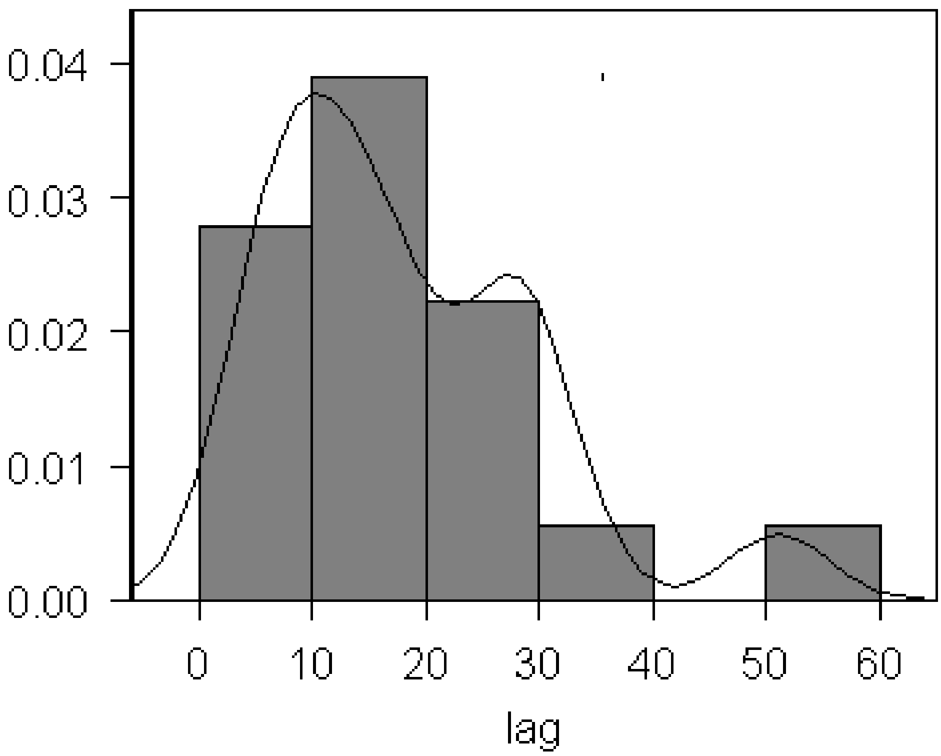
There are 18 cases of lymphoma/leukaemia and the peak in the lag curve of incidence minus exposure suggest that it is the exposure that is the cause. This graph is shown in Fig 1, attached.

The Italian researchers calculated the expected numbers of cases based on the rates in the Italian population, which are not very different from rates in the England and Wales population, which I have access to and will use. This will not introduce a significant error into the analysis. What is not known, however, is the magnitude of the "healthy worker effect".

There are three questions an epidemiologist must ask when examining the data in Table 3 in connection with a hypothesis about cause. The first is, does the development of any disease follow the exposure with a pattern that suggests a temporal clustering related to the exposure period? The second is, is the disease related to the exposure in a biologically plausible way? Third, is there a significant excess number of cases, i.e. could the result have occurred by chance? We shall examine these three questions in turn.

1. Does the development of any disease follow the exposure with a pattern that suggests a temporal clustering related to the exposure period?

It is clear from the data that there appears to be an excess of lymphoma. The increase in lymphoma, Hodgkin plus Non-Hodgkin lymphoma develops in younger cases in the period 10-20 months following their exposure period. Fig 1 shows a lag histogram and also the probability density distribution of the population in terms of the lag period in months between exposure and clinical diagnosis. There is clear development of the lymphoma following the exposure.



2. Is the disease related to the exposure in a biologically plausible way.

There is now a consensus that DU particles in the micron and sub-micron range are translocated to the lymphatic system following inhalation. Although Serbia has not been studied, there is now sufficient evidence from the two UNEP studies that DU particle contamination of Kosovo and Bosnia/Montenegro was widespread and in the latter area, direct measurement confirmed the existence of DU particles in the atmosphere some two years after the conflict. Urine tests carried out by Nick Priest for the BBC found significant levels of DU in urine samples from all test cases in Kosovo and Bosnia 18 months after the use of DU weapons, and so the contamination of the territory, the air and the people is considered proven. My own investigations and measurements of DU activity in Iraq and Kosovo have led me to believe that DU resuspension in air is a real phenomenon and I believe that the recent UNEP measurements in Montenegro confirm this. The doses from the resuspended and inhaled DU particles will affect cells in the lymphatic system and the only argument is whether these doses are sufficient to cause malignant transformation. Since these are models, they should not be allowed to influence considerations about epidemiological observation. Scientific induction demands that the observation should define the risk, and in the case of DU particle exposure the mechanism of action is still an area of contention.

3. Is there a significant excess number of cases, i.e. could the result have occurred by chance?

The age breakdown of the population at risk is given in the Italian report and is reproduced in Table 4 below which also applies the age specific incidence risk per 100,000 for men in England and Wales in 1997 for Hodgkin and non-Hodgkin lymphoma to calculate the annual numbers expected in the study population. Also calculated is the expected annual numbers of cases of cancer excluding non-malignant skin cancer. The overall rates of these diseases in the Italian population are similar to those in the England and Wales population so I do not imagine that using the England and Wales population rates rather than Italian population rates (which I do not have) will introduce a significant error.

Age group	Numbers in study group	Expected NHL (rate/100,000)	Expected HL (rate/100,000)	Expected all Cancers (rate/100,000)
15-19	121	0.002 (1.8)	0.003 (2.4)	0.02 (17.3)
20-24	13943	0.26 (1.9)	0.4 (2.9)	3.86 (27.7)
25-29	12994	0.415 (3.2)	0.59 (4.6)	4.91 (37.8)
30-34	3865	0.174 (4.5)	0.13 (3.4)	1.69 (43.9)
35-39	3703	0.21 (5.8)	0.09 (2.6)	2.24 (60.5)
40-44	2514	0.22 (8.9)	0.08 (3.3)	2.60 (103.6)
45-49	1361	0.16 (11.8)	0.03 (2.3)	2.35 (172.5)
50-54	699	0.12 (17.8)	0.016 (2.3)	2.2 (315.2)
55-59	230	0.06 (26.5)	0.007 (3.1)	1.32 (575.9)
60-64	61	0.02 (33.4)	0.009 (3.1)	0.56 (933.2)
Total	39491	1.64	1.35	21.75

Table 4 Age distribution of the Italian DU study group and the expected annual incidence of lymphoma and all cancer based on rates for the England and Wales population for 1997.

The main increase in lymphoma related to the period of exposure was in the period 0-30 months and therefore it is fair to use this period to investigate whether the increase could have occurred by chance. After all, we could wait another thirty years and do the same study, and obtain no significant increase owing to the dilution of the risk by normal incidence in the survivors after the high risk period was over.

In 30 months, table 3 shows that there were 14 cases of lymphoma made up of 4 cases of NHL and 10 of HL. The comparison of expected and observed numbers are given in Table 5 together with the Risk Ratio and cumulative Poisson p-value.

Disease	Expected	Observed	Risk Ratio	Poisson p-value
Non Hodgkin	4.1	4	0.97	NS
Hodgkin	3.38	10	2.95	0.003
Lymphoma	7.48	14	1.87	0.02

Table 5. Expected and observed numbers of lymphoma cases in Italian DU study group with statistical significance based on cumulative Poisson probability.

There appears to be a significant excess risk of lymphoma, mainly Hodgkin's disease. But this is based on a national population. We have not allowed for the healthy worker effect. As Prof. Coggon implicitly concedes, these soldiers and peacekeepers will have been very fit, and much less likely than members of the general public to become ill. There is a way we can examine this and see what effect it has on the analysis. It is clear from the data in Table 3 that the ratio of lymphoma to all cancers is anomalous. In the England and Wales population (and all other populations in Europe) lymphoma is a relatively rare condition compared with other cancers. Yet for the 30 month period, in the Italian study group, there are 14 cases of lymphoma compared with 11 cases of other cancers. Indeed the spectrum of cancer incidence in the Italian group is very strange. In Table 4 I have calculated the expected number of all cancers excluding non-malignant skin cancer per year for the study group. In the 30 month period following exposure there should be, by chance alone, in an average national group of the same population distribution 54 cancers which includes 7.48 lymphomas. But our study group is not an average group: it is a healthy group and we observe this in the total number of cases observed, only 11 cancers including 2 leukaemias) plus the 14 lymphomas. Thus the ratio of lymphoma to all cancers in the study group is 14 divided by 11 or 1.27. This ratio in an average population is 7.48 divided by 46.5 which is 0.16. It is clear that the number of lymphomas in our Italian study group in the 30 months following exposure is thus 7.9 times the value expected on the basis of a healthy population. If we extend the analysis to cover all the cases we see 16 cases of lymphoma and 19 cases of 'all cancer excluding lymphoma', a ratio of 0.84. Using the expected ratio of 0.16 for an average population we see that there is an excess of 5.25-fold in lymphoma. The 30 month period figures are summarised in Table 6.

Group	Lymphoma	All cancers except lymphoma	Ratio Lymphoma/All cancers	p-value
Italian group	14	11	1.27	
England and Wales equivalent	7.48	46.5	0.16	
Allowing for 'healthy worker'	14	1.77	7.9	<0.0000

Table 6. Using the England and Wales population ratio of lymphoma to all malignancies to calculate the expected value of lymphoma in the Italian study group in the 30-month period following exposure and allow for the 'healthy worker effect'.

Conclusions

The data support the belief that there is a significant excess risk of lymphoma in the Italian peacekeepers who served in Bosnia and Kosovo. The increase in the disease was mainly in Hodgkins lymphoma and showed as a peak in incidence between 10 and 25 months following the exposure. The excess relative risk based on the England and Wales rates in 1997 was 1.9 ($p = 0.02$) for all lymphomas and 3 ($p = 0.003$) for Hodgkin's lymphoma. This is a conclusion also agreed by the authors of the report who used a different analysis to obtain a figure of Relative Risk of lymphoma of 3.69 ($p = 0.0015$; Table 7 p 12 of Italian version of report). The relative risk from other cancers was low compared with the average population. This supported the belief that the study group was a 'healthy' group. The ratio of lymphoma to all cancers except non-melanoma skin cancer was anomalously high and this could be used to quantitatively estimate the magnitude of the effect. Allowance for the effect resulted in a relative risk from lymphoma in the 30 month period following the exposure of 7.9 ($p = 0.0000$).

The Italian study supports other anecdotal evidence of increases in types of cancer in Italian and Portuguese peacekeepers in Kosovo, and together with other evidence supports the belief that DU exposure is a risk factor in lymphoma development but other possible causes associated with tours of duty in Bosnia and Kosovo may contribute or be a main cause of the observed and reported effects. In addition, evidence supporting the dangers of DU exposure come from Gulf War veterans and the Iraqi population increases in cancer and other morbidity. The conclusions of recent review of the Italian study by Coggon are not supported by either the data or the present analysis and further investigation of Italian and other veterans is recommended.

References

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